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EXAMINER	
WHITEMAN, BRIAN A	
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1635	

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9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/818,943	Applicant(s) ERIKSSON ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 28 March 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Final Rejection

Claims 1-24 and new claim 25 are pending examination.

Applicants' traversal, amendment to claims 1-3, 5, 14, 18-20, 22-24, addition of claim 25 is acknowledged in paper no. 7.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the term "such". Correction is required. See MPEP § 608.01(b).

Claim Objections

The objection to the claims has been obviated in view of the amendment to claim 1. See page 5.

However, in view of the amended claims a new objection follows:

Claims 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 is broader than the claim it depends on (claim 1) because

of the term "a promoter" in claim 4, which is broader than the term "a suitable promoter" in the independent claim.

Claim 5 is objected to because of the following informalities: depends on claim 4. Appropriate correction is required.

Claims 1-24 and new claim 25, to which the following grounds of rejection are applicable, are pending examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 and new claim 25, as best understood, are readable on a genus of a polypeptide having PDGF-C activity or an analog thereof or a functional fragment having PDGF-C activity, wherein the genus of polypeptides having PDGF-C activity are not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of nucleotide sequences comprising a PDGF-C polypeptide or an analog thereof, or a functional fragment of PDGF-C polypeptide or an analog thereof. The as-filed specification provides sufficient description of a species of nucleotide sequences encoding a PDGF-C polypeptide set forth in SEQ ID NO: 1 or SEQ ID NO: 2.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a polypeptide having PDGF-C activity or an analog thereof or a functional fragment having PDGF-C activity as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polypeptides having PDGF-C activity or an analog or a functional fragment that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a polypeptide having PDGF-C activity or an analog thereof or a functional fragment having PDGF-C activity. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified analogs having PDGF-C activity and/or functional fragments having PDGF-C activity, and/or a polypeptide having PDGF-C activity other than the PDGF-C set forth in SEQ ID NO: 1 or the polypeptide set forth in SEQ ID NO: 2 that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by

describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed polypeptides, analogs, functional fragments that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicants assert that the rejection under lack of written description should be withdrawn because the claims are directed to a method for producing a transgenic non-human animal that over-expresses a PDGF-C polypeptide. This is significant because written description analysis for such methods is different from analysis for claims claiming the polypeptide or polynucleotides per se. The DNA or protein molecules are auxiliary to the subject matter of the claim. See In re Herschler or In re Smythe. In the instant application, the claims recite a class of known compounds (see specification, pages 7 and 8; and art of record, Li et al., 2000), which describe the active core domain of PDGF-C and histidine tagged PDGF-C constructs. In addition, the specification provides adequate written description requirement even if the analysis is under the standard when the polypeptides are claimed subject matter (See page 8, 19, and 23). Furthermore, to clarify that a distinct class of molecules is recited, applicants have amended the claims to recite the polypeptide is either a PDGF-C or analog, or a fragment thereof having PDGF-C activity. See pages 5-7.

Applicants' traversal is acknowledged and is not found persuasive for the following reasons: the starting material required to produce a transgenic non-human animal over-expressing is a polypeptide having PDGF-C activity, an analog, or a functional fragment having PDGF-C activity. Therefore, the possession of a representative number of the genus of polypeptides having PDGF-C activity listed in the claimed invention is essential for the claimed invention. Thus, the polypeptides cannot be considered auxiliary because one skilled artisan cannot envision the detailed structure of a genus of the claimed polypeptides having PDGF-C activity or an analog or a functional fragment that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

In addition, the applicants cite In re Herschler and In re Smythe. Both of these cases are not considered because neither case is applicable to the rejection set forth above because neither case provides sufficient guidance or factual evidence to provide a sufficient description of polypeptides having PDGF-C activity or an analog or a functional fragment having PDGF-C activity. More specifically, with respect to In re Herschler, which encompasses a physiologically active steroid and the reverse of the decision of the board, which decision affirmed a rejection of the claims both under 35 USC 102 and 103, this case is not applicable to the applicants' traversal because one skilled in the art would not be able to reasonably correlate from steroids to providing sufficient guidance or factual evidence for a sufficient description of a genus of polypeptides having PDGF-C activity or an analog or a functional fragment having PDGF-C activity. With respect to In re Smythe, which encompasses the affirmation of rejection of claims

for lack of written description, this case is not applicable to the applicants' traversal because one skilled in the art would not be able to reasonably correlate from inert fluid media to providing sufficient guidance or factual evidence to provide a sufficient description of a genus of polypeptides having PDGF-C activity or an analog or a functional fragment having PDGF-C activity.

Furthermore, applicants' traversal is acknowledged and is not found persuasive because the genus of nucleotide sequences that has a PDGF-C activity is not disclosed in the as-filed specification. In addition, the as-filed specification and the traversal fail to provide the essential nucleotide or amino acid residues for a representative number of sequences, wherein each sequence has an activity of PDGF-C.

The as-filed specification does not provide an adequate written description of a representative number of species of polypeptides or analogs or functional fragments having PDGF-C activity. It is apparent from the state of the prior art exemplified by Chiu that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence. This essential element that is required for an adequate description of a representative number of species as embraced by the claimed genus of PDGF-C encoded nucleic acid sequences is neither described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that any polypeptide having PDGF-C activity or analog or functional fragment having PDGF-C activity without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicant was in possession of the genus of

polypeptides having PDGF-C activity as claimed, particularly since the essential element of the coding sequence of a generic PDGF-C is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of PDGF-C encoded genes or nucleic acids on the basis of the only disclosure of one PDGF-C polypeptide set forth in SEQ ID NO: 2 or in SEQ ID NO: 1.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purpose of the 'written description' inquiry, *whatever is now claimed.*" The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

With the exception of SEQ ID NO: 1 or SEQ ID NO: 2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or the simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with al it claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only SEQ ID NO: 1 and SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Therefore, the rejection under 112 written description remains.

Claims 1-24 remain and new claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method for producing a transgenic mouse over expressing platelet-derived growth factor-C (PDGF-C) in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a pro-nuclei of a fertilized oocyte and implanting said fertilized oocyte into a pseudopregnant mouse; 2) A method for producing a transgenic mouse over expressing PDGF-C in the cardiac tissue, wherein the over-expressing results in said transgenic mouse exhibiting conditions (i) myocardial hypertrophy and (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse, the method comprising the steps of: a) introducing a nucleic acid encoding SEQ ID NO: 1, wherein said nucleic acid is operably linked to a promoter, into a cell of a mouse, wherein said cell is a mouse embryonic stem cell and injecting said embryonic stem cell into a developing mouse embryo; 3) A transgenic mouse whose genome comprises a PDGF-C polypeptide, wherein said PDGF-C polypeptide is over-expressed, wherein the overexpression of PDGF-C protein in cardiac cells of mouse results in said transgenic mouse exhibiting conditions of: (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse; 4) A progeny from the transgenic mouse of 3, wherein the progeny displays a phenotype (i) myocardial hypertrophy and; (ii) cardiac fibrosis compared to cardiac tissue of a wild type mouse; 5) A method for identifying a compound as a PDGF-C antagonist, said method comprising the steps of: a) isolating a cardiac cell from the mouse of 3, b) introducing said compound into the isolated cell

from the transgenic mouse of 3, b) monitoring gene expression of PDGF-C in said cell compared to normal gene expression of PDGF-C in an isolated cell from a wild-type mouse, c) comparing gene expression in said mouse with gene expression in a control transgenic mouse d) identifying a compound that decreases the gene expression of PDGF-C; and thereby identifying said compound as a PDGF-C antagonist; 6) A method for screening a compound for inhibition of hypertrophy, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse, c) identifying compound that decreases hypertrophy in said transgenic mice compared to the control mouse and the wild-type mouse; and thereby identifying said compound as an inhibitor of hypertrophy; 7) A method for screening a compound for inhibition of fibrosis, comprising the steps of: a) administering a pharmaceutically active amount of said compound into the transgenic mouse of 3, b) monitoring cardiac development of PDGF-C in said mouse compared to normal cardiac development in a wild-type mouse and a control transgenic mouse over-expressing PDGF-C, c) identifying compound that decreases fibrosis in said mouse compared to the control transgenic mouse and the wild type mouse; and thereby identifying said compound as an inhibitor of hypertrophy, and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a polypeptide having PDGF-C activity or an analog or a functional fragment having PDGF-C polypeptide activity), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. for use in a method for producing a transgenic non-human mammal over-expressing PDGF-C.

The specification discusses that the invention features a genus of transgenic non-human mammals, which over-expresses PDGF-C and goes on to contemplate that there are two techniques for producing the transgenic mammals (page 9, lines 25-31). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection (page 20). In addition, the as-filed specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA (pages 21-23).

The specification requires that the starting material, which is a polypeptide having PDFG-C activity or analog or functional fragment having activity, be used in a method of making a transgenic non-human mammal comprising of over-expressing PDGF-C. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (pages 20-22). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) A vector comprising the cDNA encoding PDGF-C and injected the vector into a male pro-nuclei of fertilized mouse oocytes (pages 23-24). The injected fertilized oocytes were implanted into pseudopregnant

foster mothers (page 24). Furthermore, the disclosure provides sufficient characterization of mice over-expressing PDGF-C (pages 24-30). The heart phenotype of the transgenic mice was an expansion of the cardiac interstitium, which results in myocardial hypertrophy and fibrosis (page 26). The specification contemplates that the transgenic mice can be used in a method for identifying PDGF-C antagonist, compounds that inhibit hypertrophy, and compounds that inhibit cardiac fibrosis (pages 30-31).

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. See pages 20-23 of the specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. Theriogenology, Vol. 53, pages 117-126, 2000, Polejaeva states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could be undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great

interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

> The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than mice, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic mammals for use in over-expressing PDGF-C. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any method of producing transgenic mammals over-expressing PDGF-C other than transgenic mice. However, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence encoding the PDGF-C polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any other transgenic non-human mammal than in transgenic mice.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic mammal comprising a transgenic sequence encoding PDGF-C, which over-expresses the transgenic sequence such that a phenotype occurs other than in mice. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic mammal of the invention other than mice. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic mammal over-expressing PDGF-C other than mice.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mammal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. PDGF-C) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic mammals other than transgenic mice. This is because of the art of

transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammal comprising a transgene of interest (e.g. PDGF-C); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. PDGF-C) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic mammal using microinjection of transgene into germ line and producing a transgenic mammal which comprises a transgenic sequence encoding PDGF-C and which over-expresses the protein in the transgenic mammal, and, thus, a specific resulting phenotype other than in mice.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report "transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies." See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 239-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic mammal that over-expresses PDGF-C, it would require an undue amount of experimentation to reasonably predict the results achieved in any transgenic mammal comprising a transgenic sequence encoding a PDGF-C polypeptide and which over-expresses the protein in the transgenic mammal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype other than in mice.

Furthermore, with respect to claims, which are directed to a polypeptide having PDGF-C activity or an analog or a functional fragment having PDGF-C activity used in a method for producing a transgenic mouse, which over-expresses PDGF-C, the as-filed specification does not provide sufficient guidance for one skilled in the art to make any polypeptide or analog or

functional fragment having PDGF-C activity other than polypeptide set forth in SEQ ID NO: 1 or the polypeptide set forth in SEQ ID NO: 2. The as-filed specification provides sufficient guidance for one skilled in the art to make and/or use a nucleic acid encoding the PDGF-C polypeptide set forth in SEQ ID NO: 1. However, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be enabled to reasonably correlate from an isolated nucleic acid encoding SEQ ID NOs: 1 or 2 to any other nucleic acid sequence with sequence similarity to SEQ ID NOs: 1 or 2, since at the time the application was filed, predicting any protein tertiary structure based on a protein structure was considered to be unpredictable due to significant problems in several areas. The state of the art in 1998, exemplified by Chiu et al., *Folding and Design*, Vol. 3, pg. 223-228, May 1998, Chiu displays major consideration for predicting a protein tertiary structure involve issues that include:

> Predicting the three-dimensional conformation of a correctly folded protein can be divided into two distinct steps: the construction of a fitness function to evaluate the various conformations: and the search through various possible conformations for the "best" prediction most likely to represent the native state. Neither part of this problem has proven particularly tractable. The development of a general method for the prediction of protein tertiary structure based on the protein sequence remains, unfortunately, one of the great-unsolved problems of computational biophysics (pg. 223).

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of polypeptides or analogs or functional fragments having PDGF-C activity) as recited in the claims, particularly in view of the reasons set forth above and the breadth of the claims, one skilled in the art would not have known how to make and/or use the claimed invention so that it would operate as intended, *e.g.* said transgenic nucleic acid encoding a polypeptide having PDGF-C activity for use in a method of producing a transgenic mouse that over-expresses PDGF-C.

Furthermore, with respect to the claims 1-25, which read on a method for producing a non-human transgenic animal over-expressing a polypeptide having PDGFC activity or an analog or a functional fragment having PDGFC activity, wherein in view of the breadth of the claim, the claims read on producing 3 different types of mouse 1) a transgenic mouse over-expressing a polypeptide having PDGFC activity; 2) a transgenic mouse over-expressing an analog; or 3) a transgenic mouse over-expressing a functional fragment having PDGFC activity. The specification, as discussed above, teaches how to make and/or use a transgenic mouse over-expressing a polypeptide set forth in SEQ ID NOs: 1 or 2, however the state of the art does not provide sufficient guidance for the entire breadth of the claimed invention because of the art of record set forth above. The specification states that overexpression of PDGF-C results in the development of hypertrophy and fibrosis in transgenic mice and "there are many "biological activities of PDGF-C" that can be readily tested by methods known in the art" (See page 10). In view of the breadth of the claim, the specification does not provide sufficient guidance or factual evidence for what nucleotides or amino acids are considered essential for the development of hypertrophy and fibrosis in various organs in transgenic mouse other than over-expressing SEQ ID NO: 1 or 2 and in view of this, it would require an undue amount of experimentation to reasonably extrapolate from the amino acids set forth in either SEQ ID NOs: 1 or 2 to any other polypeptide contemplated to have PDGFC activity or analog or functional fragment having PDGFC that is required to produce the desired phenotype in mice. Thus, in view of the breadth of the claim the disclosure is only enabled for to make and/or use SEQ ID NO: 1 or 2.

In addition with respect to claim 1, wherein in view of the breadth of the claim, the term cell encompassing any cell (e.g. somatic, embryonic, and germ-line) and introducing the cell into

any target site in a mouse. The state of the art, as discussed above, teaches how to use a mouse pro-nuclei or a mouse embryonic stem cell in a method of producing a transgenic mouse, however the state of the art does not provide sufficient guidance for how to use any other cell (somatic cell, e.g. lung cell, muscle cell) in a method of producing a transgenic mouse. Furthermore, the state of the art teaches that stem cells are injected into a blastocyst or a mice embryo or that a pro-nuclei cell is injected into a fertilized oocyte, however, the disclosure and the art of record do not provide sufficient guidance for how to introduce a cell into any part of a non-human animal other than injecting a pro-nuclei cell into a fertilized oocyte or a blastocyst. Thus, in view of the breadth of the claim the disclosure is only enabled for injecting a pro-nuclei of a mouse into a fertilized oocyte or injecting a genetically modified mouse embryonic stem cell into a blastocyst of a developing embryo of a mouse.

Furthermore, with respect to claims 20-21, which are directed to a method for identifying compounds as a PDGF-C antagonist, the specification and does not provide sufficient guidance for one skilled in the art to monitor the biological activity of PDGF-C in said transgenic mouse. In view of the art of record and the disclosure, one skilled in the art would reasonably be enabled for monitoring the biological activity of PDGF-C by isolating a cell from a transgenic mouse and comparing the expression of mRNA or DNA to a cell isolated from a wild-type mouse and a cell isolated from a control transgenic mouse to determine the biological activity of PDGF-C in the transgenic mouse. However, the specification and art of record do not provide sufficient guidance for one skilled in the art to reasonably correlate in vitro assays to in vivo assays without an undue amount of experimentation. The specification lacks sufficient guidance for one skilled in the art to monitor the biological activity of PDGF-C in vivo in a transgenic mouse without

isolating a cell from the mouse and comparing to other isolated cells. Thus, the claims are only enabled for a method for identifying a compound as a PDGF-C antagonist, wherein the method is an in vitro diagnostic assay.

Furthermore, with respect to claims 22, which is directed to an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the effect of a compound in a cell from a transgenic mouse over-expressing PDGF-C, the as-filed specification provides sufficient guidance for one skilled in the art to assay the cardiac effect of said compound. However, in view of the breadth of the claim, the as-filed specification lacks sufficient guidance for one skilled in the art to assay for any other effect. The specification provides sufficient guidance for one skilled in the art to identify a compound as a PDGF-C antagonist by assaying the cardiac effect of said compound on cardiac cells, but it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a cardiac effect to any other effect of a compound in any other cell. The specification does not provide sufficient guidance for what other effects (e.g. neurological) could reasonably be observed without undue experimentation. Thus, the disclosure is only enabled for one skilled in the art to make and/or use an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the cardiac effect of a compound in a cardiac cell from a transgenic mouse over-expressing PDGF-C.

In conclusion, in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material, a transgenic non-human mammal over-expressing PDGF-C, the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human mammal other than mice, the

claimed invention is only enabled for 1-7 listed above. Furthermore, the working examples for the demonstration or the reasonable correlation to the production of any transgenic mammal other than mice, in particular when the expression of the PDGF-C must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species other than mice, and the breadth of the claims drawn to any transgenic non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants assert that the rejection under 112 lack of enablement should be withdrawn because: The improper nature of the lack of written description rejection with regard to PDGF-C polypeptides has been discussed above; as of the filing date of the instant application, numerous successful examples had been reported that produced transgenic animals in animal models other than the mouse; the emphasis of the success of the ES approach in mice, however, is misplaces because other approaches have been successful (See Polejaeva et al); nothing more than routine experimentation for one skilled in the art to test cells taken from an animal to look for raised in potential protein levels in an SDS-gel; with regard to the phenotypes that may be expressed in a claimed transgenic animal, many "off the shelf" type promoters are known and readily available (page 11, lines 11-16 of the specification). See pages 7-10.

Applicants' traversal is acknowledged and is not found persuasive because in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material for producing a transgenic non-human mammal over-expressing PDGF-C, the lack of direction or sufficient guidance provided by the as-filed specification for the production of any

transgenic non-human mammal other than mice with the desired phenotype, the claimed invention is only enabled for 1-7 listed above.

The traversal is not found persuasive for the following reasons: one skilled in the art would not have known how to make and/or use the claimed invention so that it would operate as intended, e.g. for use in a method for producing a transgenic non-human mammal over-expressing PDGF-C because of the lack of written description for a genus of PDGF polypeptides, analogs, or a functional fragment having PDGF-C activity.

Even if the applicants' are able to overcome the 112 written description for a genus of PDGF-C polypeptides, analogs, or functional fragments thereof having PDGF-C activity, the applicants' traversal is still not found persuasive because the traversal and the specification do not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use the full breadth of the claimed invention.

With respect to claims, which are directed to a polypeptide having PDGF-C activity or an analog or a functional fragment having PDGF-C activity used in a method for producing a transgenic mouse, which over-expresses PDGF-C, the as-filed specification does not provide sufficient guidance for one skilled in the art to make any polypeptide or analog or functional fragment having PDGF-C activity other than polypeptide set forth in SEQ ID NO: 1 or the polypeptide set forth in SEQ ID NO: 2. However, the as-filed specification does not provide sufficient guidance for how one skilled in the art would be enabled to reasonably correlate from the polypeptide sequence of SEQ ID NOs: 1 or 2 to any other nucleic acid sequence with sequence similarity (e.g. allelic variant, functional fragment, polypeptide having PDGF-C activity), since at the time the application was filed, predicting any protein tertiary structure

based on a protein structure was considered to be unpredictable due to significant problems in several areas, see Chiu.

With respect to applicants' assertion that amending the claims to read a polypeptide or an analog or a fragment thereof having PDGF-C activity provides sufficient guidance for one skilled in the art to make and/or use the claimed invention. The specification asserts that many "biological activity of PDGF-C" can be readily tested by methods known in the art (page 10). Thus, it is readily apparent that the as-filed specification fails to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. V. Novo Nordisk A/S/, CA FC, 3/13/97, p.1005.

In addition, Ferrara et al. (WO99/47677) teaches a nucleotide sequences (VEGF-E) with 99.6% homology to applicants' SEQ ID NO: 1 and the sequence has tranquilizer, vulnery, and cardiac activity in a mammal. In view of the numerous nucleic acid sequences with homology to the polypeptide set forth in SEQ ID NO: 1 and the lack of guidance provided by the specification or applicants' traversal; it would take one skilled in the art an undue amount of experimentation to make and use any polypeptide, allelic variant, or functional fragment having PDGF-C activity without providing the essential amino acids or nucleotides required for PDGF-C activity.

Furthermore, the lack of working examples for the demonstration or the reasonable correlation to the production of any transgenic mammal other than mice, in particular when the expression of the PDGF-C must occur at a level resulting in a **corresponding phenotype**, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human

mammals of any species other than mice, and the breadth of the claims drawn to any other transgenic non-human mammal.

It is noted that the production of transgenic animals including mouse is considered conventional when using pro-nuclei injection, however, the rejection is directed to the unpredictability of the working examples for the demonstration or the reasonable correlation to the production and using of any transgenic mammal other than mice, in particular when the expression of the PDGF-C must occur at a level resulting in a **corresponding phenotype**. Furthermore, the specification has to teach how to use the transgenic animal and there could be numerous methods for using a transgenic non-human animal over-expressing PDGF-C. For example, the specification states that, "the transgenic animals of the invention are useful in both understanding the effect of over-expressing PDGF-C and as a research tool for developing compounds that will inhibit the effects caused by over-expression of PDGF-C, such as development of hypertrophy and fibrosis in various organs such as the hear (page 10)." However, in view of the art of record displaying the unpredictability of random integration of DNA into a cell's genome and transgene behavior, and the lack of guidance provided by the traversal and/or the specification for making and using transgenic non-human mammal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. PDGF-C) is not expressed at a sufficient level for a resulting phenotype).

With respect to claim 1, which reads on a non-human transgenic animal over-expressing a polypeptide having PDGF-C activity or an analog or a functional fragment having a PDGF-C,

the traversal and/or the specification do not provide sufficient guidance or factual evidence for one skilled in the art to make and/or use any cell from a non-human animal in view of the rejection set forth under 112 enablement.

Furthermore, in view of the unpredictability stated by the art of record, the traversal and/or the specification do not provide sufficient guidance and/or factual evidence for making and/or using any ES cell other than mouse. The applicants provide a journal article using rat's stem cells to produce chimeras. Iannaccone does not use the same material (genetically modified stem cells comprising a nucleic acid encoding a PDGF-C polypeptide) and/or methods as contemplated by the claimed invention. In view of art of record, producing rats with different fur color using unmodified rat stem cells does not reasonably extrapolate to use as intended by the application because of the unpredictability of using any type of stem cells other than mouse stem cells (See Rulicke).

Furthermore the traversal is not found persuasive with respect to amended claim 20 and originally filed claim 21, which are directed to a method for identifying compounds as a PDGF-C antagonist, the specification and the applicants traversal do not provide sufficient guidance and/or factual evidence for one skilled in the art to monitor the biological activity of PDGF-C in said transgenic mouse. In view of the art of record and the disclosure, one skilled in the art would reasonably be enabled for monitoring the biological activity of PDGF-C by isolating a cell from a transgenic mouse and comparing the expression of mRNA or DNA to a cell isolated from a wild-type mouse and a cell isolated from a control transgenic mouse to determine the biological activity of PDGF-C in the transgenic mouse. However, the specification lacks sufficient guidance for one skilled in the art to monitor the biological activity of PDGF-C in vivo

in a transgenic mouse without isolating a cell from the mouse and comparing to other isolated cells. Thus, the claims are only enabled for a method for identifying a compound as a PDGF-C antagonist, wherein the method is an in vitro diagnostic assay.

Furthermore the traversal is not found persuasive with respect to amended claim 22, which is directed to an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the effect of a compound in a cell from a transgenic mouse over-expressing PDGF-C, the as-filed specification provides sufficient guidance for one skilled in the art to assay the cardiac effect of said compound. However, in view of the breadth of the claim, the as-filed specification and/or the applicants' traversal lack sufficient guidance or factual evidence for one skilled in the art to assay for any other effect. The specification provides sufficient guidance for one skilled in the art to identify a compound as a PDGF-C antagonist by assaying the cardiac effect of said compound on cardiac cells, but it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a cardiac effect to any other effect of a compound in any other cell. The specification does not provide sufficient guidance for what other effects (e.g. neurological) could reasonably be observed without undue experimentation. Thus, the disclosure is only enabled for one skilled in the art to make and/or use an in vitro method for identifying a compound as a PDGF-C, said method comprising monitoring the cardiac effect of a compound in a cardiac cell from a transgenic mouse over-expressing PDGF-C.

Therefore, the rejection under 112 enablement remains.

Applicants assert that the rejection for claims 2-3, 10-17, 20, and 22-24 are overcome by the amendment to the claims and the rejection claims 10-17 for alleged indefiniteness is respectfully traversed because a survey of the issues US Patent claims reveal that both are acceptable even thought some practitioners prefer one over the other; Inasmuch as parent claim 9 embraces any number of animals, it is proper to use the indefinite article "a" or "an" to indicate the dependent claims are directed to any one of these animals, whereas the use of the definite article "the" may improperly imply that the parent claim embraces only a single animals.. See page 10.

Applicants' traversal is acknowledged and is found partially persuasive and the rejection for claims 2, 3, 20, 22-23 is withdrawn. However, the rejection for claims 10-17 and 24 remain and in view of the new claim, a new rejection follows under 112 second.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 10-17 remain and claims 1-9 and 18-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "analog having PDGF-C activity" in claims 1-25 is a relative phrase, which renders the claim indefinite. The phrase "analog having PDGF-C activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the phrase. More specifically, the disclosure does nor particularly point out and distinctly claim what analog has PDGF-C activity.

Claim 24 recite the limitation "the cardiac development". There is insufficient antecedent basis for this limitation in the claim.

The statement in claims 10-17 and new claim 25, "**an animal according to claim**" is indefinite because it does not point out which animal **an** animal is referring to in the claim. The dependent claim should state "**the** animal of claim."

Applicants' traversal is acknowledged and is not found persuasive for the following reasons: the MPEP 608.01(n) describes dependent claims, the dependent claims used under the heading "Acceptable Multiple Dependent Claim Wording" use the preamble "A gadget...". Thus, the article "A" in the preamble is acceptable according to the MPEP.
However, the claims are not multiple dependent claims. More specifically, the independent claim (claim 1), which each claim depends on has the preamble "A transgenic". Therefore, it is not apparent to one skilled in the art which animal the dependent claims are claiming. For example, claim 9 states "A transgenic", which refers to **one animal** and claim 10 states "An animal according to claim 9", which refers that the claim encompasses **more than one transgenic animal**. Suggest amending the word 'A" to the "The" in the claims.

Applicants' traversal is acknowledged and is not found persuasive for the new rejection because the traversal is not applicable to the rejection.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

Brian Whiteman
Patent Examiner, Group 1635
5/31/02

DAVE T. NGUYEN
PRIMARY EXAMINER